

## REMARKS

Claims 27, 30-33, 44, and 47-49 are currently pending in this application. Claims 27, 30-33, 44, and 47-48 are rejected under 35 U.S.C. § 103(a) for obviousness over Varesco et al. (Hum. Genet. 93:281-286, 1994; hereinafter “Varesco”) in view of Morris et al. (U.S. Patent No. 5,770,421; hereinafter “Morris”). Dependent claim 49 is objected to but would be allowable if rewritten in independent form. By this reply, Applicants amend claims 27, 32, and 47-49, add new claims 50-53, and address the rejections.

### Support for the Amendments

Support for the amendment to claims 27 and 48 and for new claims 50 and 52 is found in the specification at, e.g., page 6, line 26, through page 7, line 14. Claims 32 and 49 are amended for reasons related to clarity. Support for new claims 51 and 53 is found in the specification at, e.g., page 20, lines 1-4. No new matter is added by the amendment.

### Telephonic Interviews

Applicants wish to thank Examiner Sisson for the helpful and productive telephonic interviews of December 4, 2007, February 8, 2008, and March 12, 2008. For the reasons discussed below, Applicants believe that the subject matter of present claims 27, 30-33, 44, and 47-53 has been distinguished from the subject matter disclosed in the publications cited in the present rejection under 35 U.S.C. § 103(a).

### Rejection Under 35 U.S.C. § 103(a)

Claims 27, 30-33, 44, and 47-48 are rejected under 35 U.S.C. § 103(a) for obviousness over Varesco in view of Morris. Applicants have amended independent claims 27 and 48 to clarify that the recited methods involve the *in vitro* detection of a given, predefined pathological condition that causes disease in a tissue distinct from blood cells by detecting hybridization between 1) nucleic acid molecules from a subject being tested for the pathological condition and 2) nucleic acid molecules present in a nucleic acid library that are specific for differentially

spliced RNAs that are expressed in blood cells from human subjects known to have the pathological condition and that are characteristic of the pathological condition to be detected. In addition, present independent claims 27 and 48 recite that the nucleic acid library is capable of detecting the presence of a given, predefined pathological condition when contacted with a diverse population of nucleic acid molecules prepared from nucleated blood cells from a human subject having the given, predefined pathological condition. Thus, present independent claims 27 and 48 now clarify that hybridization between nucleic acid molecules from the blood cells of a patient to be tested for a pathological condition and nucleic acid molecules of the nucleic acid library, which are specific for differentially spliced RNAs expressed in blood cells from patients known to have the pathological condition, allows determination of the presence or absence of the pathological condition in the subject.

In contrast to the methods of present independent claims 27 and 48, and claims dependent therefrom, Varesco describes the detection of an abnormal mRNA transcript that results from a genetic mutation that is present in the genome of every cell of the patient. Expression of the abnormal mRNA transcript results in the development of colorectal adenomatous polyps. Mutations in the APC gene are also known to cause disease in blood cells (see, e.g., Wada et al., J Mol Med., 75:139-44, 1997; a copy of the abstract is provided). Thus, Varesco fails to teach or suggest a method for detecting a pathological condition of a tissue distinct from blood cells by using nucleic acid molecules obtained from blood cells.

Morris fails to remedy the deficiencies of Varesco. Morris merely discloses the detection of an abnormal genetic translocation, which results in the fusion of the NPM gene with the anaplastic lymphoma kinase (ALK) gene (see col. 1, lines 21-29); Morris clearly fails to teach or suggest the detection of differential splicing events. In any event, the translocation described in Morris causes disease in blood cells (i.e., lymphoma). Thus, Morris, like Varesco, fails to teach or suggest a method for detecting a pathological condition of a tissue distinct from blood cells by using nucleic acid molecules obtained from blood cells.

Applicants submit that the present rejection of claims 27, 30-33, 44, and 47-49 under 35 U.S.C. § 103(a) over Varesco in combination with Morris can be withdrawn and should not be applied to new claims 50-53.

### CONCLUSION

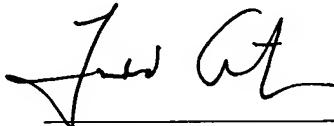
Applicants submit that the claims are now in condition for allowance, and such action is respectfully requested.

Enclosed is a Petition to extend the period for replying to the non-final Office Action for three months, to and including March 20, 2008, and a check in payment of the required extension fee.

If there are any charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

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1: [J Mol Med. 1997 Feb;75\(2\):139-44.](#)

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FULL-TEXT ARTICLE

**Molecular analysis of the adenomatous polyposis coli gene in sarcomas, hematological malignancies and noncolonic, neoplastic tissues.**

**Wada M, Miller CW, Yokota J, Lee E, Mizoguchi H, Koeffler HP.**

Division of Hematology/Oncology, Cedars-Sinai Medical Center, UCLA School of Medicine 90048-1865, USA.

Somatic mutations of the adenomatous polyposis coli (APC) gene have been frequently found in sporadic colorectal tumors, and the frequency of such mutations remain constant as tumors progress from benign adenomas to malignant cancers. Thus the mutations of the APC gene may have a major role in the early development of sporadic colorectal tumors. Whether inactivation of the APC gene accounts for other types of primary tumors is still being investigated. We investigated for APC mutations within the mutation cluster region (a 684-bp region containing most of the mutations found in colorectal tumors) in 317 samples from a wide variety of human malignant and premalignant tissues, including 40 lung cancers, 47 renal cell carcinomas, 41 osteosarcomas and 21 other types of sarcomas, 45 acute lymphoid leukemias/lymphomas, 33 acute myeloid leukemias, 27 myelodysplastic syndrome samples, and 20 chronic colitis (ulcerative colitis and Crohn's disease) associated cancers and dysplasias, and 43 human malignant cell lines. We used single-strand conformation polymorphism assay following polymerase chain reaction. Samples with abnormal assay results were reamplified and analyzed by the direct DNA sequencing method. We detected a total of two cases with a base substitution. A silent mutation was detected in a case of myelodysplastic syndrome, and a novel nonsense mutation was discovered in a colorectal cancer cell line, SW837. In summary, we did not detect any functional mutations of the APC gene in a wide variety of tumors except for a colon cancer cell line, suggesting that alterations of the APC gene do not have a major role in the development of lung and renal cancers, various types of sarcomas, or hematological malignancies.

PMID: 9083931 [PubMed - indexed for MEDLINE]

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Detection of mutations in the DNA polymerase delta gene of human sporadic colorectal cancers and colon cancer cell lines. [Int J Cancer. 1999]

Adenomatous polyposis coli gene mutations in ulcerative colitis-associated dysplasias and cancers versus sporadic colon neoplasms. [Cancer Res. 1995]

Characteristics of somatic mutation of the adenomatous polyposis coli gene in colorectal tumors. [Cancer Res. 1995]

Mutations of the adenomatous polyposis coli gene in sporadic thyroid neoplasms. [Clin Endocrinol Metab. 1994]

Reduction in alkaline sphingomyelinase in colorectal tumorigenesis is not related to the APC gene. [Int J Cancer. 2000]

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